REMARKS

Amendments to the Specification

In the last reply applicants corrected several translation errors in the specification. In support, substitute pages for the PCT translation were also provided. Upon reviewing applicants' file, it appears that not all translation errors were corrected. The amendments address further translation errors. In support a verified copy of substitute pages for the PCT translation are attached to this reply.

Furthermore, the amendment made to the specification on pages 3-4 in the Reply dated November 12, 2002, is further clarified.

Election/Restriction

The claims are amended to remove the non-elected subject matter.

Double Patenting

Applicants will attend to this provisional rejection after allowable matter is identified.

Rejections Under 35 USC 102

In the claims, R^3 is defined to not be phenyl. Support for this amendment can be found on page 8, lines 13-14, page 15, middle of the page, page 19, top of page, and on page 23, middle of the page, and in several examples, where R^3 is defined as phenyl. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See MPEP 2173.05(i) and In re Johnson, 558 F.2d 1008, 194 USPQ 187 (CCPA 1977). Thus, compounds 93668-03-2 and 88369-73-7 do not anticipate.

Compound 88369-74-8 is also not within the scope of the claims since it contains an =O group on the nitrogen of the pyridine group, i.e., on applicants' corresponding R^1 group. Accordingly, this compound does not anticipate.

The First Rejection Under 35 U.S.C. § 112, first paragraph

Claim 7 has been rejected under 35 U.S.C. § 112, first paragraph.

The Office Action appears to completely disregard the amendment made to claim 7 in the last reply and appears to recite the same rejection as made before. The rejection states, for example, that "claim 7 is drawn to a method based on KDR and/or FLT antagonism."

Previously amended claim 7 directs the claimed matter to VEGF-mediated conditions which are also specifically identified. Thus, the allegation that the claim reads on "any and all tumor, psoriasis, ..." is not correct. The claim recites "a disease or condition mediated by VEGF which is a tumor, psoriasis, arthritis ..." Accordingly, the diseases recited are ones that are mediated by VEGF. Nevertheless, applicants address the allegations from the Office Action.

As discussed in the previous reply, applicants are not asserting that persistent angiogenesis is the only cause of the various diseases identified specifically in claim 7. However, when persistent angiogenesis is the cause of the disease or condition it can be induced by the VEGF factor binding to its receptor. By inhibiting VEGF by, for example, inhibiting the kinase(s) (KDR or FLT) involved in VEGF receptor phosphorylation, one can inhibit persistent angiogenesis and therefore treat VEGF-mediated diseases/conditions. This is known as discussed on page 1 of the specification.

In an enablement rejection, first and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (1971). "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 209 USPQ 48 (1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.*

The Examiner has not established any basis to doubt objective enablement. The Examiner has also provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The enablement rejections by the Examiner are thus unfounded. The rejection therefore was improper under *In re Marzocchi*, and must be reversed for this reason alone.

The claims rejected are directed to the treatment of a variety of VEGF mediated diseases, the treatment of which are not objectively doubtable. Doubt has been held reasonable only where, for example, the invention has been characterized as "highly unusual," *In re Houghton*,

433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). Because compounds having similar therapeutic activities are known in the art, the existence of a new class of compounds having the claimed activities is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative."

The Office Action nevertheless, while referring to a recent article, alleges that anti-angiogenic agents in the treatment of cancer have a number of potential problems in a clinical trial. (Emphasis added.) The Office Action further alleges that it would pose undue experimentation to find a compound that will be "really effective" in treating cancer associated with angiogenesis based on the alleged problems encountered in the clinical trials discussed in the reference. However, this reference does not provide basis for objectively doubting the asserted utility, which is what the PTO should be concerned with. To the contrary, it specifically teaches, or at least strongly suggests, that anti-angiogenic agents are useful in the treatment of cancer since work on them is being done at the clinical trial stage. As in *Brana*,[1] 51 F.3d 1560 (Fed. Cir. 1995), the reference, even assuming the allegations regarding the reference are completely correct, which is not admitted, merely discusses problems encountered during clinical trials which becomes relevant only if applicants must prove the ultimate value in humans of their asserted utility, which is not a requirement under patent law. The Federal Circuit in *Brana* also stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Accordingly, an applicant is not required to demonstrate "treatments" of diseases that are claimed in providing an enabling disclosure. See *Brana*, supra, stating that the "stage at which an

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1 "The references cited by the Board, Pazdur and Martin, do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility."

invention in this field becomes useful is well before it is ready to be administered to humans," i.e., well before an example of treatment stage or even well before a clinical trial stage.

Additionally, applicants provide guidance by examples, which demonstrate the activity level of numerous compounds according to the invention. See pages 73-76 of the specification which show the kinase inhibition IC_{50} (in μmoles) of numerous compounds from the examples. One of ordinary skill in the art, through routine testing, can determine the activity level of any number of compounds from the claims in the same manner as the activity level of the ones tested were performed, for example. Taking this knowledge, one of ordinary skill in the art, knowing the nexus between the claimed diseases and the activity demonstrated and/or easily obtained by routine testing, can further proceed to, for example, clinical trial, etc., which of course, for patenting purposes is irrelevant.

Regarding undue experimentation, the court in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), held that the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Appellants have provided adequate guidance by, for example, providing dosage formulations, quantities of active ingredients, forms of administration, etc., and also by demonstrating in examples the activity levels of numerous claimed compounds.

Applicants also point to *Bundy*, supra, where the relevant specification disclosed only that the compounds of the invention possess activity similar to E-type prostaglandins without any examples. Nevertheless the court found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity." (Emphasis added.) Appellants have done at least that in the present case, and thus, satisfied the how-to-use requirement of section 112.

Therefore, applicants respectfully request withdrawal of this rejection.

The Second Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6 were rejected as not being enabled for preparation and use where Z and R^1 and R^1, R_a and R_b, R_c and R_d forming a bridge. The Office Action alleges that no such compounds have been made.

To clarify, R_a to R_f are groups within the definition of Z that can form bonds among each other or can form a bridge to R^1 or R^2. The specification on page 6 teaches that "If R_a-R_f form a

bridge on their own, Z represents a cycloalkyl or cycloalkenyl group. If up to two of radicals R_a-R_f form a bridge of no more than 3C atoms, and said bridge is connected to R^1, Z together with R^1 is a benzo- or hetaryl-condensed (Ar) cycloalkyl." Page 6 illustrates such groups that have bridges to R^1. There are many synthesized compounds in the specification that have structures that have a bridge to R^1. Compare the illustrated structures on page 6 to synthesized examples 2.2, 2.9, 2.13, 2.20, 2.24, etc. For an example of R_a-R_f forming a bridge on their own, where Z represents a cycloalkyl or cycloalkenyl group, see, for example, compound 2.44.

Thus, the rejection has no basis. Reconsideration is requested.

The Rejections Under 35 U.S.C. § 112, second paragraph

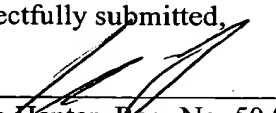
The Office Action alleges that the double bond before the N groups should be a single bond at various places in the claims while referring to $=NR^{10}$, $=NR^2$, $=NR^9$ and =N-. The "=" sign does not mean that the two bonds signified go to the same location; it merely denotes that there are two bonds from the N atom to other group(s), which can be either to the same or a different group. Reading the claims, it is readily apparent to one of ordinary skill in the art that at certain times, the "=" cannot mean that a double bond connects to a single location. Thus, the claims are clear to one of ordinary skill in the art and are thus, definite wherefore no correction is necessary.

00 The Office Action alleges that the use of "and/or" makes it difficult to determine which R group is connected to which R group to form a bond or bridge in the definition of R_a-R_f. Applicants respectfully disagree with the rejection. Even if it were "difficult" to determine the bonds and/or bridges, this would not make the claim indefinite. The use of the "and/or" language cuts down on the number of words that would have to be used to independently write out each possible bond or bridge, which would be more complex.

The Office Action alleges that it is not understood what the phrase "with R_a-R_f from Z, or to R^1, forms a bridge" means. Applicants submit that the claims are clear in that the bridge is formed with R_a-R_f, which are from the definition of Z, i.e., "from Z," or the bridge is to the R^1 group.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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